

# Vaccination and rheumatoid arthritis

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## Induction of rheumatoid arthritis by vaccination against hepatitis B—myth or reality?

Recently, medical and public interest in the safety of vaccination, particularly against hepatitis B, has been heightened by reports in medical journals and in the media of possible adverse effects, especially of suspected vaccination-induced autoimmune disorders. Although these suspected effects most commonly belong to the neurological area, a number of authors have published cases of rheumatic disease, notably rheumatoid arthritis (RA), following hepatitis B vaccination.<sup>1–10</sup> This editorial does not aim to review the relationship between vaccination and autoimmune disorders, which has already been discussed in several recent and interesting papers,<sup>11–13</sup> but to centre the discussion on the possible connection between hepatitis B vaccination and RA.

The rheumatic disorders described following hepatitis B vaccination are heterogeneous but can be divided into three groups. Firstly, transient conditions such as vasculitis, post-vaccinal arthritis or erythema nodosum might be due to the deposition of immune complexes containing viral antigen and anti-hepatitis B antibodies, as seen in some hepatitis B infections, or to hypersensitivity to components of the vaccine like thimerosal or yeast proteins.<sup>14–15</sup> Recently, the VAERS (Vaccination Adverse Events Reporting System) database (from July 1990 to August 1999) reported that hepatitis B vaccination was associated with a number of potentially serious arthritic adverse reactions, particularly in the adult female population (female/male ratio = 4.45/1).<sup>16</sup> Secondly, it was recently suggested that macrophagic myofasciitis might be induced by intramuscular injection of vaccines containing aluminium hydroxide such as hepatitis B vaccine.<sup>17</sup> Thirdly, there are reports of the onset of chronic autoimmune disease and, in particular, of RA.

Several hypotheses can be put forward for the occurrence of RA after immunisation against hepatitis B.<sup>11</sup> (1) The relation between vaccination and disease might in fact be coincidental and this possibility will be discussed later. (2) Alternatively, the vaccination might induce specific forms of disease. There are, however, no apparent differences between post-vaccinal and classical RA, which present

similar clinical and laboratory characteristics.<sup>10</sup> Moreover, as patients with post-vaccinal RA often develop joint erosions or periarticular osteoporosis and often require disease modifying antirheumatic drugs, the resemblance to classical RA does not favour this hypothesis.

(3) A more attractive view is that hepatitis B immunisation may trigger the onset of disease in subjects with underlying genetic and immunological susceptibility. Thus, some case reports describe the onset of RA following a first vaccine injection, with recurrence or worsening of the articular symptoms after a second injection. It is of interest to note that most patients with post-vaccinal RA express HLA-DR1 or HLA-DR4, or both.<sup>9,10</sup> Furthermore, the patients described by Pope *et al* shared the HLA-DRβ1 0301 and HLA-DQβ1 0201 alleles.<sup>9</sup>

### "A genetic susceptibility to RA may be activated by vaccination"

Current thinking favours the theory that RA develops in susceptible subjects in response to environmental stimuli and among the possible stimuli, infection and vaccinal immunisation have been postulated as the most likely.<sup>18</sup> An interesting case-control study of Harrison *et al* suggested that the frequency of prior immunisation (tetanus toxoid, influenza, and others) was higher among patients with inflammatory polyarthritis, including RA, than among age and sex matched controls.<sup>19</sup> These authors also observed that inflammatory polyarthritis appearing after immunisation did not seem to differ from other forms of the disease. Ferrazzi *et al* described patients in whom hepatitis A vaccination was followed by a connective tissue disorder or spondyloarthropathy,<sup>20</sup> and reports of rheumatic disease occurring after other vaccines have appeared.<sup>21</sup> The results of Harrison's study, the diverse vaccines implicated in post-immunisation polyarthritis, the variety of affections seen after hepatitis B vaccination and the resemblance between the

post-vaccinal conditions and well characterised disorders support the hypothesis that immunisation, especially to hepatitis B, may activate underlying chronic inflammatory or autoimmune disease and, in particular, RA in susceptible subjects.

However, the cases have usually been presented in the form of case reports and only a few series have been reported.<sup>9,10</sup> There are moreover no epidemiological data to support the idea that hepatitis B vaccination might induce rheumatic autoimmune disorders, especially RA. Consequently, we do not know whether there exists a causal or a coincidental relationship between RA and hepatitis B vaccination. The immunisation programmes have not shown any association between immunisation against hepatitis B and the occurrence of autoimmune disorders, including RA,<sup>22–24</sup> which suggests that there is no or only a very slight connection between the vaccination and these diseases. In addition, several recent epidemiological studies did not show any relationship between hepatitis B vaccination and multiple sclerosis,<sup>25,26</sup> systemic lupus erythematosus, or RA.<sup>27</sup> One case-control study, conducted using the British General Practitioners Research Database (GPRD), included 2814 patients with RA and 27 040 controls. Vaccination against hepatitis B had been performed in 52 patients and 449 controls, the odds ratio was 1.1 (95% CI 0.8 to 1.4)<sup>27</sup> and a complementary subgroup analysis failed to detect any significant association between RA and hepatitis B immunisation. Hence the recent increase in published cases might simply be due to the universal immunisation programmes in which, for example, more than one third of the French population was vaccinated in the past few years.<sup>28</sup>

Thus, there are conflicting data with, on the one hand, negative results from immunisation programmes and epidemiological studies and, on the other hand, case reports which are sometimes very suggestive. These results might provide evidence to support the somewhat provoking hypothesis of the protective effect of infections and immunisations.<sup>13</sup> In fact, the microbial environment can shape the immune response and, in particular, tolerance phenomena, which would explain why, in practice, immunisations against microbes may reduce the risk of the occurrence of autoimmune disorders. Nevertheless, in the case of existing autoimmune disease, a non-specific immunisation might activate the inflammatory reaction, leading in RA to an exacerbation of the articular manifestations. Although further epidemiological studies will be necessary to clarify these phenomena, one may conclude at present that if hepatitis B vaccination can trigger RA, it is an infrequent event.

Hence we still require answers to several questions, such as "Do we need to stop the universal immunisation programmes?", or "Is it dangerous to vaccinate patients with RA against hepatitis B?" Because the immunisation programmes and epidemiological studies indicate that there is no or only a very slight association between hepatitis B vaccination and autoimmune or chronic inflammatory rheumatic disorders, the benefits of the vaccine probably outweigh the risks of possible side effects. Universal hepatitis B vaccination indeed significantly reduced the virus carrier and infection rates among children and adolescents in a hyperendemic area.<sup>29</sup> In Italy, the annual incidence of acute hepatitis B virus infection decreased from 5.4 to 2.9/10<sup>5</sup> inhabitants between 1990 and 1998 (and from 17.3 to 4.2/10<sup>5</sup> in 15–24 year olds), suggesting that universal immunisation does reduce the incidence of infection.<sup>30</sup> In France, it has been estimated that 3–29 cases of fulminant hepatitis and 12–147 cases of cirrhosis or hepatocellular carcinoma would be avoided in an fictive cohort of 800 000 vaccinated 11 year old pre-adolescents, up until the age of 30.<sup>28</sup> Thus, in our opinion, universal immunisation has to go on.

There remains the question of hepatitis B vaccination in some individual subjects, such as patients with RA. Before attempting to reply, one should recall that this matter has been raised for other vaccinations, notably against influenza.<sup>31, 32</sup> Different studies have shown that such immunisations induce no significant RA, apart from possibly certain exceptions like the vaccine against measles.<sup>33</sup>

The report of Elkayam *et al* in this issue of the *Annals of the Rheumatic Diseases* constitutes a first step in the reply to this question with respect to RA. In this study hepatitis B vaccination in patients with RA was not associated with any appreciable deterioration of the clinical or laboratory measures of disease activity.<sup>34</sup> However, before claiming that immunisation against hepatitis B is safe in patients with RA, these reassuring results need to be confirmed in larger scale studies. In the meantime, vaccination should be proposed cautiously in selected cases, taking into account the individual risk of developing hepatitis B and the fact that the vaccine elicits a

protective antibody response in only 66% of patients with RA.<sup>34</sup>

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